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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte ROBERT HALEY, ALAN VARLEY,
and ROBERT MUNFORD

Appeal 2009-013357
Application 10/039,171
Technology Center 1600

Decided: March 16, 2010

Before DEMETRA J. MILLS, FRANCISCO C. PRATS, and
JEFFREY N. FREDMAN, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to methods for protecting cells from organophosphate toxin. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

Statement of the Case

Background

"Paraoxonase is a serum enzyme that hydrolyzes organophosphate compounds, aromatic carboxylic acid esters and carbamates" (Spec. 2, ll. 10-11). The Specification teaches that organophosphates "are widely used in agriculture as insecticides and are also manufactured as chemical warfare nerve agents" (Spec. 2, ll. 25-26). According to the Specification, "Paraoxonase activity in mammals is important for the detoxification of OPs [organophosphates]" (Spec. 3, ll. 13-14).

The Specification teaches "the use of paraoxonase 1 (PON1) genes to protect cells from toxins" (Spec. 2, ll. 7-8).

The Claims

Claims 1-5, 9-25, and 36-43 are on appeal. Claim 1 is representative and reads as follows:

> 1. A method of protecting a cell from organophosphate toxin comprising:
>
> (a) identifying a cell at risk of exposure or exposed to an organophosphate toxin;
>
> (b) providing an expression cassette comprising a promoter active in said cell and a gene encoding PON1 under the control of said promoter; and
>
> (c) transferring said expression cassette into said cell under conditions permitting expression of PON1;
>
> wherein said expression cassette expresses PON1 in said cell, providing protection from said organophosphate toxin.

The prior art

The Examiner relies on the following prior art references to show unpatentability:

Scheffler	US 5,721,118	Feb. 24, 1998
Radtke	US 6,521,226 B1	Feb. 18, 2003

Li et al., *Paraoxonase protects against chlorpyrifos toxicity in mice*, 76 TOXICOLOGY LETTERS 219-226 (1995).

Humbert et al., *The molecular basis of the human serum paraoxonase activity polymorphism*, 3 NATURE GENETICS 73-76 (1993).

Davies et al., *The effect of the human serum paraoxonase polymorphism is reversed with diazoxon, soman and sarin*, 14 NATURE GENETICS 334-336 (1996).

Adkins et al., *Molecular Basis for the Polymorphic Forms of Human Serum Paraoxonase/Arylesterase: Glutamine or Arginine at Position 191, for the Respective A or B Allozymes*, 52 AM. J. HUMAN GENETICS 598-608 (1993).

The issues

A. The Examiner rejected claims 1-5, 10-13, 17-25, 37-39, and 43 under 35 U.S.C. § 103(a) as obvious over Radtke, Li, Davies, Adkins, and Humbert (Ans. 3-7).

B. The Examiner rejected claims 1, 9, 14-16, 21, 36, and 40-42 under 35 U.S.C. § 103(a) as obvious over Radtke, Li, Davies, Adkins, Humbert, and Scheffler (Ans. 7-9).

A. 35 U.S.C. § 103(a) over Radtke, Li, Davies, Adkins, and Humbert

The Examiner concludes that it would have been obvious to the ordinary artisan "to combine the teaching of Radtke taken with Li, Adkins,

Humbert, and Davies, namely to identify a cell or subject exposed to an organophosphate toxin and express PON 1 in a cell or subject exposed to the organophosphate toxin" (Ans. 5).

Appellants argue that "the examiner cannot point to *either* an adequate motivation in the cited art or the field in general to support the combination of references, nor is there any indication that one of skill in the art would have found anything like a *reasonable* likelihood of success in practicing the invention" (App. Br. 5). Appellants argue that "Davies' demonstration of substrate specificity for PON1 Q and R on serum samples tested *in vitro* was not sufficient to demonstrate that boosting PON1 Q and R isoenzyme concentrations *in vivo* would successfully protect against OP poisoning" (*id.* at 6).

Appellants argue that "the U.S. PTO is estopped in this case from taking the position that gene therapy is a predictable art . . . for the simple reason that the present examiner has already gone on record in this prosecution that gene therapy *is*, in fact, unpredictable" (*id.* at 8). Appellants also argue that "there is clearly no 'finite number of identified, predictable solutions' from which the skilled artisan could choose" (*id.* at 10).

In view of these conflicting positions, we frame the obviousness issue before us as follows:

Have Appellants demonstrated that the Examiner erred in finding that the combination of Radtke, Li, Davies, Adkins, and Humbert suggest protecting a cell from organophosphate toxins by transferring a PON1 expression cassette into the cell to express PON1?

Findings of Fact

1. Radtke teaches that paraoxonase "is well-known to be involved in the hydrolysis of several organo-phosphate insecticides" (Radtke, col. 2, ll. 37-39).

2. Radtke teaches that prior patents "are directed to a human paraoxonase gene, its associated vectors and transformed host cells and their use to detoxify organophosphates in vivo and for a neuroprotective effect" (Radtke, col. 2, ll. 46-49).

3. Radtke teaches "the use of DNA sequences encoding PON-1 in gene therapy applications" (Radtke, col. 8, ll. 27-28).

4. Radtke teaches that "[l]ocal delivery of PON-1 using gene therapy may provide the therapeutic agent to the target area. Both in vitro and in vivo gene therapy methodologies are contemplated. Several methods for transferring potentially therapeutic genes to defined cell populations are known" (Radtke, col. 8, ll. 37-41).

5. Radtke teaches that "any suitable gene therapy vector containing PON-1 DNA or DNA of muteins of PON-1 may be used in accordance with this embodiment. The techniques for constructing such a vector are known. . . . Introduction of the PON-1 DNA-containing vector to the target site may be accomplished using known techniques" (Radtke, col. 9, ll. 34-42).

6. Li teaches that "administration of exogenous paraoxonase to rats has been shown to offer protection against the toxicity of PO [paraoxon] and CPO [chlorpyrifos-oxon]" (Li 220, col. 2).

7. Li "addressed the questions of whether exogenous paraoxonase would affect the toxicity of a phosphorothioate, in addition to the oxon, and would be useful as a therapeutic agent when administered after organophosphate poisoning" (Li 220, col. 2).

8. Li teaches that "2 types of administration were chosen for the present experiments: i.v. injection, which elevated mouse serum enzyme activity toward CPO by 35-fold at 30 min with a half-life of 6 h; and a combination of i.v. plus i.p. injections which still increased enzyme activity toward CPO by 35-fold, but also increased the half-life to 30 h" (Li 221, col. 2).

9. Li teaches "[t]o examine whether the increased serum paraoxonase levels would offer protection against cholinesterase inhibition cause by CPO, the chemical was applied dermally, since this is the primary route of exposure to organophosphorus insecticides" (Li 221, col. 2).

10. Li teaches that "3 groups of animals were used: a control group, which received acetone only; a CPO group, which received CPO dissolved in acetone; and a CPO + CPOase group, which was given paraoxonase via i.v. injection, followed after 30 min by CPO" (Li 221, col. 2).

11. Li teaches that the "results of these studies indicate that purified rabbit paraoxonase injected into mice increases the serum activity and protects mice from CPS toxicity. Paraoxonase was able to prevent the decrease in cholinesterase activity when it was administered before, as well as after, CPS poisoning" (Li 223, col. 2).

12. Davies teaches that the "high density lipoprotein (HDL)-associated enzyme paraoxonase (PON1) contributes significantly to the

detoxication of several OPs [organophosphorus compounds]" (Davies 334, col. 1).

13. Davies teaches that the "Arg_{192} (R_{192}) PON1 isoform hydrolyses paraoxon rapidly, while the Gln_{192} (Q_{191}) isoform hydrolyses paraoxon slowly" (Davies 334, col. 1).

Principles of Law

The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) secondary considerations of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). The Supreme Court has emphasized that "the [obviousness] analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007).

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.* at 416. "If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability." *Id.* at 417.

Analysis

Li "addressed the questions of whether exogenous paraoxonase would affect the toxicity of a phosphorothioate, in addition to the oxon, and would be useful as a therapeutic agent when administered after organo-phosphate poisoning" (Li 220, col. 2; FF 7). Li teaches that "purified rabbit

paraoxonase injected into mice increases the serum activity and protects mice from CPS toxicity. Paraoxonase was able to prevent the decrease in cholinesterase activity when it was administered before, as well as after, CPS poisoning" (Li 223, col. 2; FF 11). Thus, Li determined that exogenous paraoxonase is a useful therapeutic agent for treatment of organo-phosphate poisoning (FF 6-11).

Radtke teaches that paraoxonase is known to hydrolyze organophosphate insecticides and has been suggested as an agent to detoxify organophosphates in vivo (FF 1-2). Radtke teaches that paraoxonase may be delivered to patients by gene therapy techniques with the PON1 expression vector (FF 3-5). Davies teaches the human PON1 polymorphisms (FF 12-13).

In applying the *KSR* standard of obviousness to the findings of fact, we agree with the Examiner that it would have been obvious to replace Li's intravenous administration of PON1 as a therapeutic agent treating organo-phosphate poisoning (FF 7) with delivery of the PON1 expression vector by gene therapy as taught by Radtke since Li expressly suggests that PON1 is a useful therapeutic agent for organophosphate poisoning and since Radtke teaches that "[l]ocal delivery of PON-1 using gene therapy may provide the therapeutic agent to the target area. Both in vitro and in vivo gene therapy methodologies are contemplated. Several methods for transferring potentially therapeutic genes to defined cell populations are known" (Radtke, col. 8, ll. 37-41; FF 4).

Appellants argue that "the examiner cannot point to *either* an adequate motivation in the cited art or the field in general to support the

combination of references, nor is there any indication that one of skill in the art would have found anything like a *reasonable* likelihood of success in practicing the invention" (App. Br. 5).

We are not persuaded. Li provides a specific reason to increase PON1 levels in patients experiencing organophosphate poisoning (FF 7), and Radtke provides several ways in which PON1 levels may be increased in patients (FF 1-5). Li explains that the "results of these studies indicate that purified rabbit paraoxonase injected into mice increases the serum activity and protects mice from CPS toxicity. Paraoxonase was able to prevent the decrease in cholinesterase activity when it was administered before, as well as after, CPS poisoning" (Li 223, col. 2; FF 11).

The combination of Radtke and Li is precisely the sort of combination envisioned by *KSR*, where the known method of increasing PON1 levels by gene therapy taught by Radtke is used to increase PON1 levels to protect from organophosphate poisoning as taught by Li (FF 1-11).

Appellants argue that "Davies' demonstration of substrate specificity for PON1 Q and R on serum samples tested *in vitro* was not sufficient to demonstrate that boosting PON1 Q and R isoenzyme concentrations *in vivo* would successfully protect against OP poisoning" (App. Br. 6). Appellants also argue that "there is clearly no 'finite number of identified, predictable solutions' from which the skilled artisan could choose" (App. Br. 10).

We are not persuaded. We conclude that Davies and Li together provide a "reasonable expectation of success," not Davies alone. Li experimentally demonstrates that increased PON1 enzyme levels function to treat organophosphate poisoning (FF 8-11). Radtke relies upon known

vectors and techniques for gene therapy (FF 4-5). Appellants have provided no evidence which would suggest that Li or Radtke are unpredictable. *Kubin* stated that "[r]esponding to concerns about uncertainty in the prior art influencing the purported success of the claimed combination, this court [in *O'Farrell*] stated: '[o]bviousness does not require absolute predictability of success … *all that is required is a reasonable expectation of success*.'" *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009) (citing *In re O'Farrell*, 853 F.2d 894, 903-904 (Fed. Cir. 1988)).

We conclude that given the direct suggestion in the prior art of Li that increasing the levels of the PON1 enzyme would be effective in treating organophosphate poisoning (FF 7-11), there would have been a reasonable expectation of success in treating organophosphate poisoning by increasing the levels of PON1 using the gene therapy methods of Radtke (FF 1-5). The prior art provides a finite number of ways to deliver PON1, as required by Li for treatment of organophosphate poisoning, including i.v. or i.p. administration (FF 8) as well as gene therapy administration (FF 2-5).

Appellants argue that "none of these papers address the question of whether *boosting both PON1 Q or R* will protect differentially from OP exposure *in vivo*. There simply were too many unknowns that had not been addressed, any of which could have made the concept fail" (App. Br. 7).

We are not persuaded. The claim at issue, Claim 1, requires that an "expression cassette expresses PON1 in said cell, providing protection from said organophosphate toxin." There is no requirement in Claim 1 regarding differential effectiveness of PON1 Q or R. Further, Davies teaches that the different PON1 isoforms perform differently (FF 12-13). We decline to read

a limitation requiring a specific PON1 form into claim 1. "[L]imitations are not to be read into the claims from the specification." *In re Van Geuns*, 988 F.2d 1181, 1184 (Fed. Cir. 1993) (citing *In re Zletz*, 893 F.2d 319, 321 (Fed. Cir. 1989)).

Appellants argue that "the U.S. PTO is estopped in this case from taking the position that gene therapy is a predictable art . . . for the simple reason that the present examiner has already gone on record in this prosecution that gene therapy *is*, in fact, unpredictable" (App. Br. 8).

We are not persuaded. While ideally the Examiner's position would remain consistent throughout prosecution, the Examiner is permitted to change his viewpoint regarding the patentability of the claims as prosecution progresses. *See In re Ruschig*, 379 F.2d 990, 992-993 (CCPA 1967) ("The words of Judge Garrett in *In re Ellis*, 86 F.2d 412, 24 CCPA 759, which appellants found quoted in *In re Becker*, 101 F.2d 557, 26 CCPA 922, fairly depict the present situation, which is not much different from that prevailing in 1936, There is nothing unusual, certainly, about an examiner changing his viewpoint as to the patentability of claims as the prosecution of a case progresses, and, so long as the rules of Patent Office practice are duly complied with, an applicant has no legal ground for complaint because of such change in view. The life of a patent solicitor has always been a hard one.")

Conclusion of Law

Appellants have not demonstrated that the Examiner erred in finding that the combination of Radtke, Li, Davies, Adkins, and Humbert suggest

protecting a cell from organophosphate toxins by transferring a PON1 expression cassette into the cell to express PON1.

B. 35 U.S.C. § 103(a) over Radtke, Li, Davies, Adkins, Humbert, and Scheffler

The Examiner finds it obvious to modify the method of Radtke, Li, Davies, Adkins, Humbert with the promoters and tail of Scheffler since "[o]ne of ordinary skill in the art would have been motivated to combine the teaching for protecting the mRNA from exonucleases and for proper polyadenylation of the gene transcript" (Ans. 8).

The Examiner provides sound fact-based reasoning for combining Scheffler with Radtke, Li, Davies, Adkins, and Humbert. As Appellants do not identify any material defect in the Examiner's reasoning, and only argues the underlying rejection of Radtke, Li, Davies, Adkins, and Humbert, which we affirmed above, we affirm the this rejection for the reasons stated by the Examiner.

SUMMARY

In summary, we affirm the rejection of claim 1 under 35 U.S.C. § 103(a) as obvious over Radtke, Li, Davies, Adkins, and Humbert. Pursuant to 37 C.F.R. § 41.37(c)(1)(vii)(2006), we also affirm the rejection of claims 2-5, 10-13, 17-25, 37-39, and 43 as these claims were not argued separately.

We affirm the rejection of claim 1 under 35 U.S.C. § 103(a) as obvious over Radtke, Li, Davies, Adkins, Humbert, and Scheffler. Pursuant to 37 C.F.R. § 41.37(c)(1)(vii)(2006), we also affirm the rejection of claims 9, 14-16, 21, 36, and 40-42 as these claims were not argued separately.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv)(2006).

AFFIRMED

cdc

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